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Relation Between Myocardial Infarct Location and Stroke

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Objectives. **We sought to compare the likelihood of stroke in patients with anterior versus nonanterior myocardial infarction.**

Background. **The association between anterior infarction and left ventricular thrombus has led to the assumption that embolization from thrombi is an important cause of stroke in patients with anterior infarction. We hypothesized that if anterior infarction is a cause of left ventricular thrombi, the number of strokes should be disproportionately higher in patients with anterior than nonanterior infarction.**

Methods. **We performed a retrospective analysis of 2,466 patients randomized from day 3 to day 15 after infarction as part of a multicenter placebo-controlled study of diltiazem to prevent cardiac death or myocardial infarction. Any acute focal cerebral disorder resulting in localizing findings characterized as a stroke or transient ischemic attack was considered an event.**

Results. **Of 91 events during a follow-up period of 12 to 52 months, 23 (3.2%) occurred in 724 patients with an anterior and 68 (3.9%) in 1,742 patients with a nonanterior myocardial infarction (relative risk 0.81; 95% confidence interval 0.51 to 1.30). Power analysis revealed that the negativity of the study was not the result of inadequate sample size. Life table analysis showed no difference in cumulative event rate ($p = 0.42$) according to site of infarction. Cox regression analysis showed that of 10 clinical covariates, only systolic blood pressure was predictive of stroke ($p < 0.001$). The use of warfarin did not contribute to the model. Finally, the addition of site of infarction (anterior vs. nonanterior) did not contribute significantly to the Cox model.**

Conclusions. **Although there is a significant incidence of stroke after acute myocardial infarction, there is no relation between the occurrence of stroke and site of infarction. These data do not support the presumed causal relation between anterior myocardial infarction, thrombus and stroke.**

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The risk of stroke is increased after myocardial infarction (1–4). The close association between anterior myocardial infarction and left ventricular thrombus has led to the assumption that embolization from left ventricular thrombi is an important cause of stroke in these postinfarction patients. Indeed, several reviews (5–8) recommend obtaining an echocardiogram in patients with an anterior myocardial infarction and providing anticoagulant therapy if thrombus is found, although this procedure is not accepted universally (9). Yet, prospective studies have reported varying degrees of success with the use of anticoagulants to prevent thrombus (10–14) or reduce the likelihood of stroke (12–18).

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The present study was undertaken to examine the relation between myocardial infarction site and the incidence of stroke. We hypothesized that if thrombus formation in patients with anterior infarction is an important cause of stroke, patients with anterior infarction should have an increased incidence of stroke.

Methods

The study protocol involved a retrospective review of the baseline and follow-up data in all 2,466 patients randomized in the Multicenter Diltiazem Postinfarction Trial (MDPIT) from February 17, 1983 to June 30, 1986. The recruitment procedure and inclusion and exclusion criteria have been previously reported (19). In brief, men or women 25 to 75 years old who were admitted to the hospital and subsequently documented to have had an acute myocardial infarction were eligible. Patients were excluded if there was evidence of ongoing cardiogenic shock, pulmonary hypertension, high degree atrioventricular block or other conditions likely to reduce survival. Randomization took place during hospital days 3 to 15 (median day 8) from the time of onset of the myocardial infarction.

All patients were followed up for 12 to 52 months (average 25 months). Patients were seen by the investigator or clinical coordinator, or both, at periodic intervals throughout the trial. The MDPIT follow-up schedule consisted of five

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Table 1. Clinical Characteristics by Myocardial Infarct Site

Covariate (no. of patients with anterior, nonanterior infarction)	Site of MI (%)		p Value
	Anterior	Nonanterior	
Age ≥60 yr (724, 1,740)	50	51	0.795
Previous MI (723, 1,739)	25	20	0.002
NYHA class II–IV (724, 1,740)	19	18	0.553
History of hypertension (723, 1,739)	38	38	0.880
Insulin-dependent diabetes (724, 1,740)	9	8	0.243
Cigarette smoking (721, 1,727)	46	50	0.055
Cardiac findings			
Systolic BP <100 mm Hg (722, 1,734)	2	5	0.001
Bibasilar pulmonary rales (721, 1,733)	48	36	< 0.001
Creatine kinase ≥619 U (724, 1,739)	79	62	< 0.001
Atrial fibrillation (724, 1,740)	9	8	0.350
EF <40% (649, 1,508)	56	17	< 0.001
Thrombolysis (at index MI) (724, 1,740)	12	7	< 0.001
Treatment (at discharge) (724, 1,740)			
Aspirin	22	24	0.145
Beta-adrenergic blocking agents	49	56	0.002
Digitalis	23	10	< 0.001
Dipyridamole	8	7	0.504
Other antiplatelet agents	9	6	0.003
Reinfarction (before CVA) (724, 1,740)	0.28	0.34	0.785
Warfarin (at discharge) (724, 1,740)	19	4	< 0.001
Stroke/TIA (724, 1,740)*	3	4	0.381

*Total number of cerebrovascular events during follow-up (see text). BP = blood pressure; CVA = cerebrovascular accident; EF = ejection fraction; MI = myocardial infarction; NYHA class = New York Heart Association functional class; TIA = transient ischemic attack.

visits in the first year (an initial visit at 1 month followed by a visit every 3 months), then a visit every 4 months until study closure. Data retrieval at the clinic visit consisted of an interval medical and cardiac history, review of concurrent medications and physical examinations.

During these visits any adverse experiences or intervening medical conditions, or both, were noted and described on the clinical record forms. Stroke was not coded separately but included as either an adverse event or an interval medical event. As a result, 1,731 medical follow-up reports had to be reviewed. This review was performed by two of us (D.S. and B.S.) without knowledge of the site of the index myocardial infarction.

Definitions. A stroke was defined as an acute focal cerebral disorder that resulted in localizing findings characterized by either the patient's physician or the clinical investigator as a cerebrovascular accident. If the duration of symptoms was <24 h, the episode was defined as a transient ischemic attack (20). Nonlocalizing symptoms, such as dizziness, giddiness or wooziness, or involuntary movements, such as limb shaking, were not classified as transient ischemic attacks (20). Because this study was not prospectively designed, confirmation with computed tomography, encephalography and other procedures was not always available and was generally not recorded in the patient data.

The diagnosis of acute myocardial infarction required serum enzyme confirmation: an MB isoenzyme fraction >4% of total creatine kinase (CK) or a qualitatively positive MB band; an elevation of total lactic dehydrogenase (LDH) with abnormal reversal of the LDH_1/LDH_2 ratio, or an elevation of ≥2 times normal of CK, serum glutamic oxaloacetic transaminase or LDH in the coronary care unit with a clinically consistent pattern. Acute anterior wall myocardial infarction was defined as Q waves appearing in leads V_1 to V_4; absence of new Q waves in these leads identified patients with nonanterior myocardial infarction (19). The latter group included patients with inferior or posterior Q wave infarction (61%) and those with non-Q wave infarction (39%), defined as elevated serum enzyme levels consistent with infarction without Q waves (19).

Statistical analysis. Univariate analysis was performed to determine the relation between baseline clinical variables and infarct site (Table 1). A model was then constructed using Cox regression analysis with the occurrence of stroke or transient ischemic attack as the dependent variable (21). All covariates with a p value ≤ 0.10 were forced into the model. The use of warfarin was added to the model to determine its contribution, and it was maintained in the model regardless of its p value. The final model was constructed by adding infarct site to the model (21). Results are expressed as hazard ratio with 95% confidence limits. A power analysis was performed to determine the possibility of a beta error (22). The effect of infarct site on time to end point was examined with the method of Kaplan and Meier. The log-rank statistic was used to compare Kaplan-Meier curves. Summary odds ratios were determined with the technique of Mantel and Haenszel (22).

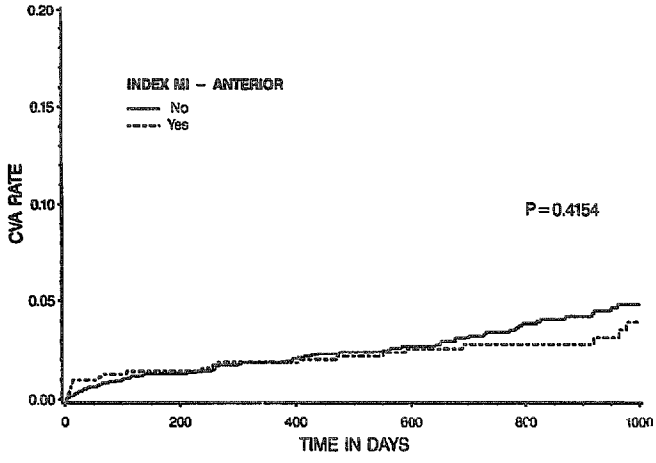

Figure 1. Kaplan-Meier survival curves for likelihood of a cerebrovascular event (CVA), defined as stroke or transient ischemic attack, in patients with anterior or nonanterior myocardial infarction (MI) at the time of enrollment.

Results

Patient characteristics (Table 1). A total of 91 patients had a stroke (n = 75) or a transient ischemic attack (n = 16) during the follow-up period. There were 47 events (3.8%) in the placebo group and 44 (3.6%) in the diltiazem group. Because of the near identity of these two groups, their data could be combined and all results reflect the total group of MDPIT patients with an event.

Patients with anterior infarction were more likely to have had a previous infarction, a lower systolic blood pressure, bibasilar pulmonary rales, higher peak CK level and lower ejection fraction. They were also more often treated with thrombolysis at the time of admission with the index myocardial infarction as well as more likely to be treated with digitalis, antiplatelet agents or warfarin at hospital discharge.

Incidence of stroke and transient ischemic attack by infarct site (Fig. 1). During the entire follow-up period, a total of 23 (3.2%) of the 724 patients with an anterior wall myocardial infarction had a stroke or transient ischemic attack compared with 68 (3.9%) of 1,742 patients with a nonanterior myocardial infarction (relative risk 0.82; 95% confidence interval [CI] 0.55 to 1.30). Power analysis revealed that this study had an 86% chance of detecting a relative risk of stroke of 1.5 in patients with anterior versus nonanterior infarction. When the patients with nonanterior infarction were classified into those with inferior or posterolateral Q waves and those with non-Q wave infarction, the likelihood of stroke was 3.5% and 4.9%, respectively. Figure 1 shows the Kaplan-Meier life table event rate for patients with anterior and nonanterior myocardial infarction. As is evident, no significant difference exists (p = 0.42 by log-rank test). When analyzed by infarct site and treatment with placebo or diltiazem, the findings were essentially the same (p = 0.35).

Multivariate analysis (Table 2). Stepwise multivariate Cox analysis was used to determine variables that were predictive of stroke and transient ischemic attack. Of the clinical covariates, only systolic blood pressure was predictive ($p < 0.001$). Warfarin did not contribute significantly to the model. Patients with anterior infarction had a stroke rate similar to that of patients with nonanterior infarction both before and after adjustment for warfarin therapy.

Table 2. Factors Associated With Stroke or Transient Ischemic Attack After Myocardial Infarction

Covariates	Hazard Ratio (95% CI)	p Value
Systolic BP* (on admission to CCU)	1.014 (1.007 to 1.021)	< 0.001
Warfarin	0.930 (0.397 to 2.179)	NS
Anterior infarction	0.825 (0.508 to 1.340)	NS

*The hazard ratio for systolic blood pressure (BP) is per unit increase in blood pressure. Thus, when compared with a patient with a systolic blood pressure of 100 mm Hg, a patient with a systolic blood pressure of 150 mm Hg would have a hazard ratio of 1.014^{50} (=1.97). CCU = coronary care unit; CI = confidence interval.

Discussion

The present study does not support the hypothesis that anterior infarction is associated with an increased risk over that of any other location for stroke after myocardial infarction. Strikingly, 3.9% of patients with a nonanterior wall myocardial infarction had a stroke compared with 3.2% of patients with an anterior wall myocardial infarction. This finding, which included adjustment for warfarin therapy, challenges the currently accepted strategy of preventing stroke by selecting patients for anticoagulant therapy on the basis of the finding of thrombus on echocardiography and limiting the screening process to those with anterior infarction (5–8).

Anticoagulation and thrombus formation (Table 3). Echocardiographic studies of the relation between anterior myocardial infarction, thrombus and stroke differ in methodology, study patients, timing of echocardiography, therapy (some including thrombolytic agents) and follow-up. With these limitations in mind, pooling these studies shows that the likelihood of thrombus and embolization in patients with anterior infarction is high whether or not anticoagulants are used (Table 3). In four studies, patients were randomized to receive either anticoagulants or placebo, although thrombolytic agents were sometimes used (11–14). Two studies (11,12) showed benefit, whereas two (13,14) showed no effect on left ventricular thrombus formation. When the four studies (11–14) were combined, no anticoagulation was associated with an increased risk of thrombus of 1.86 (95% CI 1.22 to 2.82).

Thrombolytic agents have been reported to reduce thrombus formation (27,31) or to have no effect (14,18,29,32). However, because anticoagulants are often used concur-

Table 3. Effect of Anticoagulation on Thrombus Formation and Embolic Events in Patients With Anterior Wall Myocardial Infarction

Study	No. of Patients Without Anticoagulation			No. of Patients With Anticoagulation		
	Total No.	No. With Thrombus	No. With Emboli	Total No.	No. With Thrombus	No. With Emboli
Nonrandomized Pooled Studies						
Ref. 10, 15–18, 23–32	653	169 (26%)	31* (4.7%)	497	203 (41%)	24† (4.8%)
Randomized Trials of Anticoagulation and Left Ventricular Thrombus						
Vecchio et al. (14)	86	26	1	94	25	0
SCATI trial (12)	93	34	2	107	19	0
Gueret et al. (13)	25	13	1	21	8	1
Johannessen et al. (11)	21	7	2	21	0	1
Total‡	225	80 (36%)	6 (2.6%)	243	52 (21%)	2 (0.8%)

*21 strokes and 10 noncerebral emboli. †20 strokes and 4 noncerebral emboli. ‡Cumulative odds ratio of thrombus in patients without anticoagulation versus patients with anticoagulation is 1.86 (95% confidence interval 1.22 to 2.82) with a chi-square of 8.36 with 1 degree of freedom.

rently, any benefit may not reflect the effect of thrombolytic agents (14).

The ability of anticoagulation to prevent stroke is also difficult to assess because of inadequate controls and a relative paucity of embolic events (Table 3). In the present study, warfarin was used in only 19% of patients with anterior infarction, raising the possibility of a type 2 error to explain the lack of contribution of warfarin to the model.

Effect of anticoagulation on stroke in postinfarction patients. The role of anticoagulation in patients after acute myocardial infarction has been the subject of numerous studies. Although stroke has generally not been a primary prospectively defined end point, we used previously published analyses (33–35) and a search of MEDLINE to find those randomized studies in which the incidence of stroke could be determined (Table 4) (36–44). As assessed with use of a cumulative odds ratio and the Mantel-Haenszel test (22), the risk of stroke was 2.05 (95% CI 1.5 to 2.8) in patients randomized to placebo versus anticoagulation. Left unresolved is the role of aspirin relative to coumadin in this setting (45).

Predictors of stroke after myocardial infarction. Thompson and Robinson (2) reported that 9 of 13 strokes were associated with anterolateral infarction, whereas Pullicino et al. (46) reported that 10 of 19 were associated with anterior infarction. However, neither group provided data on the likelihood of stroke in patients with anterior compared with nonanterior infarct locations. An elevated fibrinogen level (1), atrial fibrillation (3) and diabetes and hypertension (46) have also been found predictive of stroke. We found only systolic blood pressure predictive of stroke (Table 1).

Dexter et al. (4) found a higher than expected rate of stroke, particularly in the 1st 2 months after myocardial infarction. Our study also shows a relatively higher rate within the 1st 2 months, with 18 of 91 strokes occurring during this period. However, the rates were similar for patients with anterior and nonanterior myocardial infarction (Fig. 1).

Table 4. Analysis of Randomized Studies of Anticoagulation After Myocardial Infarction: Incidence of Stroke

Study	Control Group		Anticoagulation Group	
	Total No.	No. With Stroke	Total No.	No. With Stroke
MRC (36)	188	1	195	3
Wasserman et al. (37)	70	1	77	0
Lovell et al. (38)	240	13	172	2
Ritland et al. (39)	101	2	97	0
MRC (40)	715	18	712	8
Drapkin and Merskey (41)	391	9	745	13
VA Coop (42)	499	16	500	4
Sixty Plus Reinfarction (43)	439	21	439	13
Smith et al. (44)	607	44	607	20
Total*	3,250	125	3,544	63

*Summary odds ratio of stroke in patients in control groups compared with patients treated with anticoagulation is 2.05 (95% confidence interval 1.50 to 2.80) with a chi-square of 20.6 with 1 degree of freedom. MRC = Medical Research Council; VA Coop = Veterans Affairs cooperative study.

Limitations of the study. This was a retrospective study and we were unable to classify the strokes by mechanism. Other studies (1–4,40–44) similarly did not attempt to distinguish between thrombotic or embolic stroke. Also, the likelihood of hemorrhagic stroke in patients not receiving anticoagulants is extremely low and thus unlikely to have affected our results (43,44).

The failure to find statistical significance does not entirely exclude a difference. As seen in Table 4, no anticoagulation was associated with an odds ratio of 2.05 for stroke in patients after myocardial infarction. By using the lower limit of the 95% confidence interval as a guide to a clinically important relative risk, we found an 86% chance of detecting a relative risk of 1.5 in our population size. Thus, the negative outcome is not the result of inadequate sample size.

The close follow-up of the patients, which included regular histories and physical examinations, makes it unlikely that strokes were missed. The lack of echocardiographic confirmation of thrombus would be of concern; however, the finding that anterior myocardial infarction is associated with an even lower rate of stroke than is nonanterior infarction combined with the known rarity of thrombus in the absence of anterior infarction (13,16,24,30) makes this limitation of minor concern. Also, although some patients might have been excluded from the study because of an early in-hospital stroke, the incidence of such early strokes is quite small and this factor is unlikely to have altered the conclusions (11–14).

Conclusions. Our data confirm that stroke is a significant problem after myocardial infarction. However, limiting therapy to patients with anterior infarction would have failed to prevent more than half of the cerebrovascular events seen in our patients. Clearly, further studies are needed to determine the mechanism of these events. Unfortunately, no diagnostic criteria exist that reliably separate embolic strokes from those with other mechanisms, such as cerebrovascular atherosclerosis (9). Until such criteria are available, review of the published data does suggest a role for anticoagulation even though our findings do not support a specific therapy. The exact place of this strategy in relation to other interventions remains to be determined with randomized trials (45).

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